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Assessment of Coronary Stenoses by Myocardial Perfusion Imaging During Pharmacologic Coronary Vasodilation. VII. Validation of Coronary Flow Reserve as a Single Integrated Functional Measure of Stenosis Severity Reflecting All Its Geometric Dimensions

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The purpose of this study was to determine whether coronary flow reserve measured by flow meter correlated with or could be predicted by quantitative coronary arteriography accounting for all dimensions of a coronary artery stenosis. Five dogs were chronically instrumented with an inflatable stenosing cuff, a Doppler flow velocity meter, proximal and distal coronary artery catheters and aortic and pulmonary artery catheters. For 18 stenoses over a wide range of severity, orthogonal coronary arteriograms were analyzed quantitatively at rest to predict coronary flow reserve based on fluid dynamic equations. The X-ray–predicted coronary flow reserve correlated closely with that measured directly by implanted flowmeter with an r value of 0.91, a regression equation of X-ray–predicted coronary flow reserve = 1.08 (measured coronary flow reserve) − 0.08 and 95% confidence limits (±2 SD) of 0.66. Neither percent diameter narrowing alone nor absolute stenosis diameter alone correlated well with measured coronary flow reserve. Results confirm that coronary flow reserve is a single integrated measure of coronary stenosis severity reflecting all its geometric dimensions. Flow reserve correlated closely with and was accurately predicted by quantitative coronary arteriography taking into account all stenosis dimensions. This study establishes the theoretical and experimental basis for using coronary flow reserve as a single, integrated functional measure of stenosis severity reflecting all of its geometric characteristics.

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The functional significance of coronary artery stenoses derives from their effects on coronary blood flow. Assessing their functional significance from arteriograms is difficult, in part because of the variety of shapes they present. Stenoses may be long, short, segmental, diffuse, symmetric, asymmetric or tapering. No single anatomic criterion or measurement can describe their appearance or account for this variety of shapes having hemodynamic effects. Consequently, the concept of coronary flow reserve as a functional measure of stenosis severity was initially proposed by Gould et al. (1) in 1974 on the basis of empiric observations and was subsequently developed as a physiologic diagnostic method (2–12). Because the measurement of percent diameter narrowing was the accepted standard for describing stenosis severity at that time, the concept of coronary flow reserve was initially demonstrated by relating the decrease in coronary flow reserve to percent diameter narrowing for experimental coronary stenoses having relatively uniform length and absolute diameter. Many others (13–21) have confirmed these findings and showed the effects of changing specific geometric dimensions of a stenosis on coronary flow reserve. We have also demonstrated (22) the validity of quantitative coronary arteriography for predicting the functional pressure-flow characteristics of stenoses if *all* the dimensions of the lesion are taken into account, including percent diameter narrowing, absolute diameter, length and asymmetry of the stenosis. However, no previous report has validated the relation between all the dimensions of tapering arterial stenoses on arteriograms with coronary flow reserve.

Recent reports (23–25) have described a poor correlation between coronary flow reserve and percent diameter narrowing in human coronary artery disease and have proposed absolute diameter as a better measure of stenosis severity. However, these studies did not use biplane arteriographic

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views or did not utilize complete fluid dynamic equations accounting for all the geometric dimensions of the stenoses. Therefore, the use of absolute stenosis diameter as a measure of severity remains open to question. However, results of these studies confirm those of previous reports (1–14,26) indicating that percent diameter narrowing alone is not a satisfactory measure of stenosis severity.

There are several reasons for defining the relation between coronary flow reserve and stenosis configuration. Bomberger et al. (27) demonstrated that experimental stenoses over a prolonged period of time may undergo "molding" in vivo whereby lesions may change dimensions. A stenosis may become longer with worsening absolute diameter but less severe percent diameter narrowing, it may become more or less eccentric, or it may become more severe in one part but less severe in another part. Assessment of severity or changing severity therefore requires some measurement that reflects all the dimensions of a stenosis.

Even with complete quantitative coronary arteriography (28), a description of altered configuration is difficult if the stenosis dimensions change in opposite directions. To obtain an integrated, single measure of stenosis severity, Brown et al. (28) initially developed quantitative coronary arteriography to calculate stenosis resistance from all dimensions based on fluid dynamic equations. Although Brown and coworkers (29–31) demonstrated the value of quantitative arteriography for clinical research, calculated resistance is difficult to relate to common physiologic measurements of pressure and flow. Therefore, Gould et al. (4,12,22) used the pressure gradient-flow relations of a stenosis, either directly measured or derived from quantitative coronary arteriography, as a means of quantifying severity in more physiologic terms. In either case, the use of stenosis resistance or of pressure-flow relations is oriented toward fluid dynamics and is somewhat alien to physiology and medicine. Their use, therefore, is not easily assimilated into a clinical or a standard physiologically oriented research laboratory.

Consequently, we have proposed coronary flow reserve as a single measure of stenosis severity which is conceptually more physiologically oriented and more easily measured in the physiology laboratory by flow meter or radiolabeled microspheres. With the current development of positron emission tomography into a practical and affordable clinical method for assessing perfusion, the noninvasive determination of coronary flow reserve in humans now also appears feasible. Although our initial studies beginning some years ago indicated the potential value of measuring coronary flow reserve, there has been no rigorous, systematic theoretical or experimental proof that coronary flow reserve reflects the effects of all of the combined, integrated dimensions of a coronary artery stenosis.

A major conceptual difficulty in assessing the effect of a coronary stenosis on blood flow is that myocardial perfusion is an integrated response of an anatomic-hemodynamic system in which the coronary stenosis is but one component. The description of the anatomic component cannot alone describe the behavior of the total system. Therefore, the approach we took was that of component testing, whereby the stenosis was quantified from geometry as an isolated part of the total system by imposing standardized conditions. In this regard, our approach does not conceptually differ from the testing of an isolated component of an electronic circuit. The information so gained describes the stenosis as an isolated part and as an integrated unit of the whole system.

Accordingly, the approach to this problem requires consideration of two different basic concepts about how stenosis severity is quantified. The first considers the stenotic coronary vascular system as an entire integrated system in which coronary flow reserve depends not only on stenosis configuration but also on aortic pressure, coronary vascular tone, collateral flow, normal coronary flow reserve in the absence of a stenosis and the strength of the coronary vasodilator stimulus. The second basic approach considers the anatomic stenosis as a component separate from the overall coronary vascular system such that its effects can be quantified independently of all these other variables in the system. For coronary flow reserve, a total system response, to correlate with component characteristics (that is, stenosis configuration), other variables affecting coronary flow reserve must be accounted for or standardized. The relation between stenosis configuration and functional effects of other variables can be understood only by separately analzying responses of the components of the system as well as the total system. The purpose of this report is to provide the theoretical basis and experimental validation for using coronary flow reserve as a single measure of stenosis severity accounting for all the geometric characteristics of the lesion. It therefore establishes the relation between functional or physiologic and anatomic descriptors of stenosis severity.

Methods

Surgical preparation. Five male field hounds weighing 22 to 28 kg were anesthetized with intravenous thiopental sodium and a mixture of nitrous oxide and methoxyflurane. The left circumflex coronary artery was dissected free through a sterile left thoracotomy. A small tapered tygon (polyvinyl chloride) catheter was implanted at the origin of the left circumflex artery for injection of contrast medium to obtain coronary arteriograms to measure proximal coronary perfusion pressure. A Doppler flow velocity transducer was placed around the artery distal to the proximal coronary catheter tip. Just distal to the Doppler transducer a saline solution-filled circumferential balloon constrictor was sutured in place. A second tygon catheter was inserted in the distal main circumflex artery before major branches for measurement of coronary pressure distal to the constrictor.

Dogs were treated with dipyridamole, 100 mg and aspirin, 600 mg for 2 days preoperatively and for 10 days after surgery to prevent formation of platelet clots on the catheters in the postoperative period. Catheters were flushed daily and filled with heparin. The coronary catheter construction and implantation techniques used in this laboratory and the conditions and characteristics of the animal model have been described in detail previously (32).

Instrumentation. Instantaneous mean cross-sectional flow velocity in the circumflex artery was measured with a continuous wave directional Doppler unit (L and M Electronics) operating at 8 to 9 MHz processed through a zero crossing detector with analog output proportional to the Doppler shift. The construction and calibration of the Doppler transducer has also been described previously (32). These transducers had a linear response from zero flow velocity up to the maximal measured value of 156 cm/s (600 ml/min through a 3 mm intradermal tube) with maximal Doppler shifts of up to 12 kc and signal to noise ratios of 50:1 to 100:1 both in vitro and in vivo.

Proximal and distal coronary pressures on either side of the constrictor were measured with Bio-Tec BT-70 pressure transducers, and differential pressures were recorded simultaneously using a differential pressure gauge (National Semiconductor Corporation, part no. Lx1701D) mounted in a plastic manifold to which the BT-70 transducers were also attached. Needle obturators, stopcocks and plastic parts were filled by immersion under sterile saline solution in a vacuum chamber to remove micro air bubbles and maximize frequency response. The response of the Bio-Tech catheter manometer system was flat (+5%) to 15 Hz with debubbled saline solution and that of the differential gauge with two simultaneous pressures applied to catheters used for implantation was flat to 30 Hz. For each experiment, pressure calibrations were recorded with 100 mm Hg pressure applied by mercury column to the coronary and differential transducers at the beginning and end of each study.

A standard lead II electrocardiogram, mean and instantaneous phasic flow, proximal and distal coronary pressure and differential coronary pressure were recorded on an Electronics for Medicine DR 12 physiologic recorder with a direct writer and a Honeywell 7600 tape recorder for analogue to digital computer conversion and subsequent analysis. In two of the animals differential pressure was obtained by subtracting the proximal and distal coronary pressure outputs from the tape recorder using a differential operational amplifier circuit with zero and gain adjustment. There was no difference in differential pressure values obtained by either method within a given experiment.

Coronary arteriograms were obtained by injecting radiopaque contrast medium (Renografin-76) into the proximal coronary catheter while triggering exposure of a single spot film from the electrocardiogram at mid-diastole. The injection/X-ray sequence was automated and precisely controlled using a timing circuit triggered by the R wave. The contrast medium was injected using a Thermodilution Injector #3700 (OMP Lab, Incorporated) modified to inject from an energized solenoid triggered from the electrocardiogram. The injector was powered with compressed air regulated to inject the contrast medium through the catheter at a flow rate not exceeding the coronary artery flow of the dog. Using this system less than 2 cc of contrast medium produced adequate filling for visualization of the stenotic region as well as proximal and distal normal sections of the circumflex artery. X-ray films were taken with a General Electric Maxiray 100 tube with a 0.3 mm focal spot, a 6.5° target angle and a 26 inch (66.04 cm) tube to film distance. Exposures were at 1/60 or 1/30 second, 200 mA, at 90 to 116 kV using Ultra Detail, Cronex 4, Dupont 3 X-ray film and either Ultra Detail phosphor Radelain cassettes or Kodak X-Omatic cassettes with regular intensifying screens. The entire system had a resolution of 11 line pairs per millimeter or 215 line pairs per inch.

Protocol. The dogs were positioned on their right side for biplane X-ray. Some animals were lightly sedated with xylazine (1 mg/kg body weight intramuscularly) to facilitate bradycardia and a stable position during the X-ray. During a 5 minute rest period initial flow and pressure calibrations were made and the flow response to a 10 second total occlusion was recorded. The coronary constrictor was then expanded with saline solution under pressures up to 1,000 mm Hg (20 psi) depending on the severity of stenosis desired. The expansion pressure was held constant at the chosen level by a water-sealed ball valve, in line with an automatic pressure regulator attached to a compressed air source.

The stenosis was allowed to stabilize for 20 minutes. Biplane X-ray films were taken during baseline flow conditions in the left posterior and left anterior oblique views. The two X-ray films were taken sequentially and separated by at least 3 minutes such that flow and heart rate had returned to baseline values before the second X-ray film was taken. In preliminary studies, repeated X-ray films in the same plane demonstrated return of all dimensions to control baseline at 3 minutes. The pressure and flow velocity transducers were recalibrated and baseline control recordings were made of the electrocardiogram, coronary flow velocity and proximal, distal and differential coronary pressures. A dose of 0.4 to 0.8 ml of papaverine in a concentration of 2.0 mg/ml was injected as a bolus through the distal coronary catheter to produce a transient increase in flow while phasic pressures and flow velocity were recorded. Transducer calibrations were verified at the end of data collection.

X-ray frames were automatically digitized utilizing a Spatial Data System, Eyecom II in which X-ray films were scanned by a video camera on-line with a VAX 11/780 computer. The dimensions of each stenosis were determined by a previously validated automated border recognition al-

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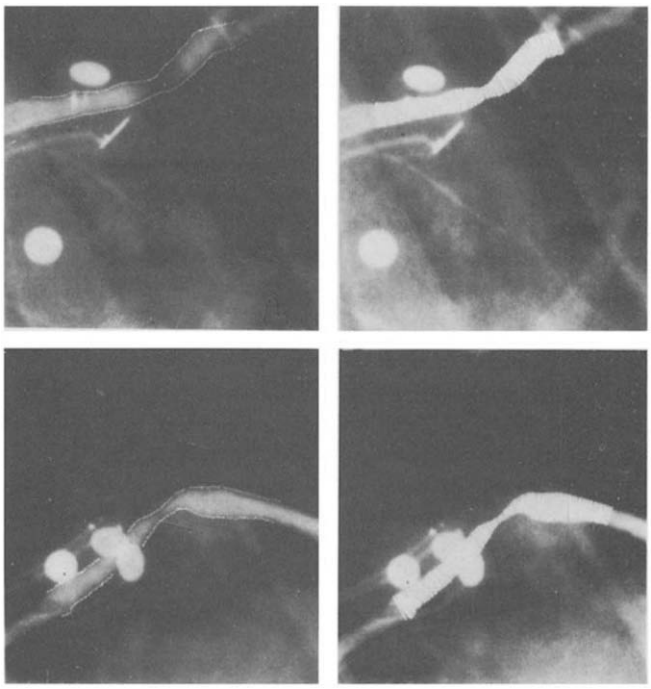


Figure 1. Orthogonal coronary arteriograms showing the automated border identification and diameter determinations as previously described (12,22).

gorithm as well as by an integrated density technique developed in this laboratory (33,34) (Fig. 1). Stenosis dimensions were determined from automated border tracings of stenoses on paired biplane images of coronary arteries with an implanted steel ball as a size reference using a previously described computer program (12,22). This program uses an adaptation of fluid dynamic equations developed and validated in vitro by Young and coworkers (13,15,35–38), adapted for tapering stenoses and X-ray analysis by Brown et al. (28) and validated in vivo by Gould et al. (12,22). The program corrected for pincushion distortion and absolute size to produce a true scale, three-dimensional characterization of the vessel and stenotic segment by matching center lines of the individual biplane projections and assuming the vessel cross section to be ellipsoidal. A hard copy printout included stenosis dimensions, the cross-sectional area of the vessel at the center of the Doppler flow probe and the computer reconstruction of the digitized vessels in each view.

The fluid dynamic equations used for predicting pressure loss across the stenosis (ΔP) in terms of coronary flow velocity or volume flow have been described previously (4,12,22) and may be *conceptually* written as follows:

$$\Delta P = \frac{8\pi\mu L}{A_s}\left(\frac{A_n}{A_s}\right) V + \frac{\rho}{2}\left(\frac{A_n}{A_s} - 1\right)^2 V^2,$$

$$\text{or } \Delta P = FV + SV^2 \quad (1)$$

$$\Delta P = \frac{8\pi\mu L}{A_s}\left(\frac{1}{A_s}\right) Q + \frac{\rho}{2}\left(\frac{1}{A_s} - \frac{1}{A_n}\right)^2 Q^2,$$

$$\text{or } \Delta P = fQ + sQ^2, \quad (2)$$

where μ = absolute blood viscosity, L = stenosis length, A_n = the cross-sectional area of the normal artery, A_s = the cross-sectional area of the stenotic segment, V = flow velocity, ρ = blood density, Q = volume flow, F and S = the coefficients of pressure loss due to viscous friction and exit separation, respectively, in the velocity equation 1 and f and s = corresponding coefficients in the flow equation 2. These equations have been adapted for tapering stenoses by integrating the length effects as previously described (12,22). Because biplane views are obtained as well as integrated gray scale density across the artery, asymmetry and nonellipsoidal arterial cross sections are accounted for. Exit shape has been previously shown to be negligible (12,22) and pressure losses due to pulsatile flow are negligible for stenoses of 50% or greater diameter narrowing (35–37). Eccentricity does not have an important effect on the functional significance of a stenosis and therefore does not need to be accounted for (38).

Prediction of coronary flow reserve. The theory and equations for predicting coronary flow reserve from X-ray–determined configuration of a coronary artery stenosis are derived in the Appendix and are shown schematically in Figure 2. The coronary pressure distal to a stenosis (P_c) is plotted on the vertical axis. Coronary artery flow is plotted on the horizontal axis as a ratio to normal flow at rest ($Q/Q_{n,r}$). The dash and dot line plots the relation between coronary perfusion pressure and coronary flow under conditions of maximal coronary vasodilators as documented experimentally by Bache and Schwartz (39). It describes the pressure-flow relation of the coronary vascular bed at maximal vasodilation. That is, it gives the maximal flow possible after maximal coronary vasodilation for a given perfusion pressure (P_c). P_v is the coronary pressure at zero flow or the back pressure of the completely occluded coronary artery; P_a is aortic pressure. For a normal, nonstenotic coronary artery, the perfusion pressure is aortic pressure and the normal maximal increase in coronary flow was assumed to be five times flow at rest (35) at a mean aortic pressure of 100 mm Hg, as shown by the dotted line.

The solid line in Figure 2 is a plot of the relation between distal coronary pressure (P_c) and flow (expressed as a ratio to control flow at rest) after coronary vasodilators in the presence of a stenosis. The solid line is the graphic plot of the equation at the bottom of the diagram derived in the Appendix. The terms A and B are related to stenosis geometry as follows: A = (f) ($Q_{n,r}$) and B = (s) ($Q^2_{n,r}$). The coefficients f and s are described earlier. Thus, for a given stenosis the relation between P_c and flow ($Q/Q_{n,r}$) is determined by measuring mean aortic pressure (P_a), the coeffi-

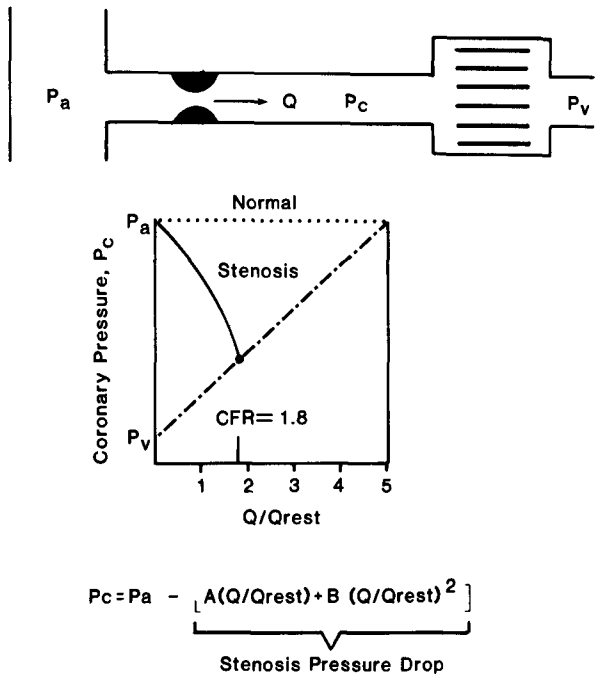


Figure 2. Top, Schematic of a stenotic coronary artery and distal bed. P_a = aortic pressure, Q = coronary flow, P_c = distal coronary perfusion pressure and P_v = effective coronary back pressure. **Middle**, In this graph, P_c is plotted on the **vertical axis** and coronary artery flow (Q) is plotted on the **horizontal axis** as a ratio to normal flow at rest (Q/Qrest). The **dash and dot line** plots the relation between coronary perfusion pressure and coronary flow under conditions of maximal coronary vasodilation in the presence of a stenosis as previously documented experimentally (39). The **solid line** is a plot of the relation between P_c (coronary pressure distal to the stenosis) and flow in the presence of a stenosis. This **solid line** is the graphic plot of the equation at the bottom of the figure derived in the Appendix. A and B are terms related to stenosis geometry. CFR = coronary flow reserve.

cients f and s from X-ray film geometry and normal flow at rest ($Q_{n,r}$) (or flow velocity because the diameter of the artery is known from the X-ray film). With known values of P_a, f, s and $Q_{n,r}$ the solid line can be plotted for any stenosis of given configuration.

Coronary flow reserve for a particular stenosis. The point at which the solid curved line (characteristic of the stenosis) intersects the linear dash and dot line (the maximal flow possible for a given coronary perfusion pressure under conditions of maximal coronary vasodilation) gives the coronary flow reserve for that particular stenosis at that particular pressure. For the example shown, the solid line intersects the dash and dot line at a coronary flow reserve of 1.8. Therefore, the maximal flow achievable for that stenosis at that aortic pressure is 1.8 times flow at rest or coronary flow reserve of 1.8. The distal coronary perfusion pressure (P_c) is about one-third the aortic pressure at that point.

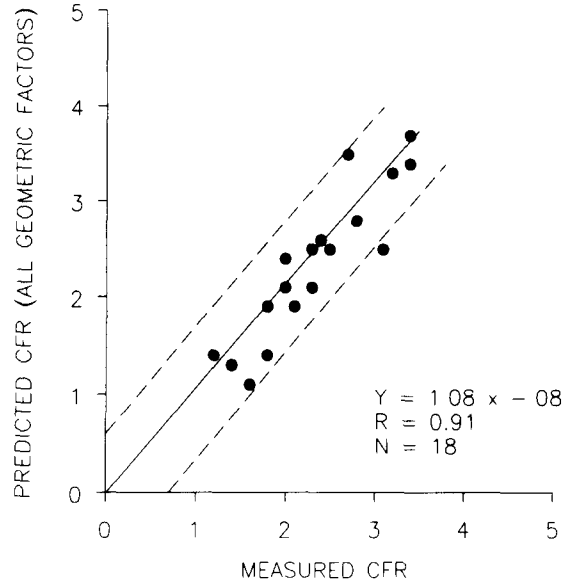
Measurements. Thus, for each stenosis in this study, P_a was directly measured as mean aortic pressure; f and s were determined by quantitative analysis of coronary arteriograms as previously described (12,24). Flow velocity at rest for medium-sized arteries 3 to 5 mm in diameter in a number of species have been observed to be 10 to 20 cm/s (mean 15) (40) confirmed in our own laboratory (4). Because coronary flow velocity at rest cannot be measured clinically by noninvasive means, we assumed a flow velocity at rest of 15 cm/s; the validity of this assumption is justified on the basis of published data and on the accuracy of the X-ray–predicted compared with directly measured coronary flow reserve, described in the Results section. With values of P_a, f, s and $Q_{n,r}$, a diagram giving X-ray–predicted coronary flow reserve like that in Figure 2 was plotted for each stenosis on the computer analysis printout. For every stenosis, coronary flow reserve was also measured directly by flowmeter and compared with that predicted from X-ray film dimensions.

Statistics. For 18 stenoses the directly measured and the X-ray–predicted coronary flow reserve were compared by regression analysis. The 95% confidence limits are shown by dashed lines on either side of the regression line (Fig. 3) (41).

Results

Figure 3 shows the correlation between X-ray–predicted and directly measured coronary flow reserve. The X-ray–predicted coronary flow reserve (CFR) correlated closely with that measured directly by flowmeter with an r value

Figure 3. Relation between the X-ray–predicted and directly measured coronary flow reserve (CFR) for 18 stenoses. The **dashed lines** indicate 95% confidence limits (±2 SD).



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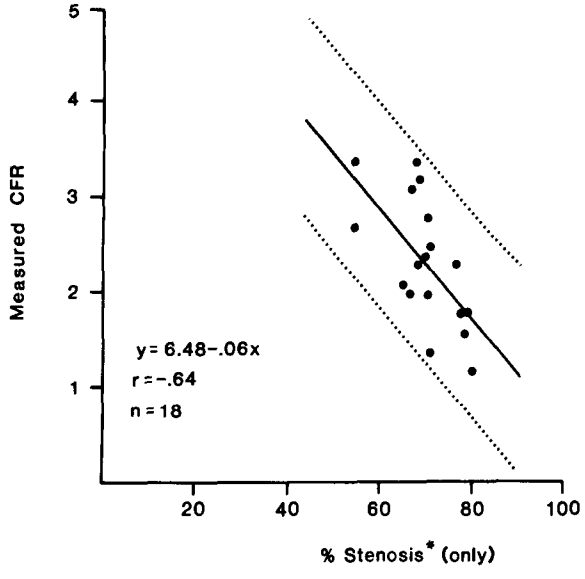
of 0.91, a regression equation of X-ray–predicted CFR = 1.08 (measured CFR) − 0.08 and 95% confidence limits (±2 SD) of 0.66 (1 SD = 0.33).

Figure 4 correlates experimentally measured coronary flow reserve with the most severe percent diameter stenosis of orthogonal X-ray views without accounting for other geometric dimensions of absolute diameter or length. The correlation is relatively poor with wide confidence limits.

Figure 5 relates experimentally measured coronary flow reserve with the absolute cross-sectional area of the artery without accounting for length (L) or percent narrowing. Although a rough correlation is apparent, it does not approximate the theoretically correct relations for a stenosis with a length of L/D = 2 (where normal diameter [D] is 4 mm) or for an orifice stenosis in a different sized artery with L/D = 0.01 (where normal diameter is 2 mm). The absolute diameter of the normal segment of artery is also important. For example, an absolute stenosis cross-sectional area of 0.5 mm^2 in a small coronary artery would not have much effect on coronary flow reserve (upper solid line) because the normal artery is small. However, this same stenosis cross-sectional area in a larger artery would be a severe narrowing that decreased coronary flow reserve markedly (Fig. 5, lower solid line). Thus, the use of absolute stenosis diameter or minimal stenosis lumen area as a measure of stenosis severity as recently reported (23–25) may also be inappropriate as a measure of stenosis severity. Our results suggest that consideration of one dimension, either percent narrowing or absolute minimal lumen area alone, is inadequate to predict coronary flow reserve, whereas consideration of all dimensions predicts coronary flow reserve accurately.

Figure 4. Relation between measured coronary flow reserve (CFR) and the most severe percent diameter stenosis of orthogonal X-ray views without accounting for the other configurational dimensions of absolute diameter or length. The correlation is relatively poor with wide confidence limits. *Most severe diameter reduction from two views.



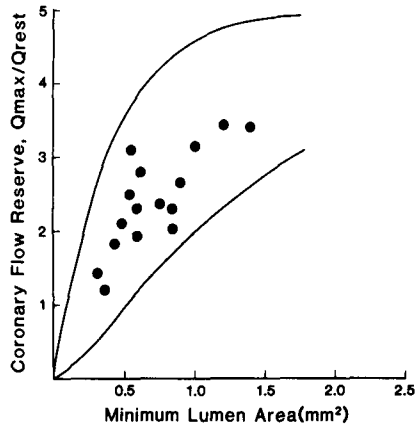


Figure 5. Relation between experimentally measured coronary flow reserve and the absolute cross-sectional area of the artery (**dots**) without accounting for length or percent narrowing (see text).

Discussion

This study demonstrates how the various anatomic descriptors of a coronary stenosis may be logically integrated to form a single, meaningful measure of its functional severity, that is, coronary flow reserve. However, it is important to recognize that myocardial perfusion is dependent on many factors besides proximal coronary stenosis, such as aortic pressure, the vasodilatory capabilities of the myocardial vessels and collateral blood flow. In this perspective, the coronary stenosis represents but one component of the anatomic-physiologic system in which myocardial perfusion depends on the response of the total system. Thus, when myocardial perfusion is impaired, a variety of possible causes exist. It is necessary, therefore, to address these other physiologic factors.

Physiologic variables. The relative importance of these physiologic variables depends on what question one wishes to ask about stenosis severity, which in turn depends on a total systems or a component analysis. For example, consider two patients with geometrically identical coronary stenoses under identical physiologic conditions except that aortic pressure is lower in one than the other. That patient with lower aortic pressure will have a lower coronary flow reserve due to a lower perfusion pressure (Fig. 2). At one extreme, if he were dead, his coronary flow reserve would be zero despite identical stenoses. Therefore, to compare stenoses in these two patients, one would need to calculate the expected coronary flow reserve under assumed standardized conditions of aortic pressure, such as 100 mm Hg,

even if one of the patients did not actually have a measured mean aortic pressure of 100 mm Hg.

Similarly, one of those two patients might not be responsive to coronary vasodilators such that his normal maximal coronary flow in the absence of stenosis would be only three times resting control at normal aortic pressure rather than five times. A stenosis that limited coronary flow to four times levels at rest would cause no limitation to flow in that case because distal vascular bed resistance would be higher than the resistance caused by the stenosis The distal bed resistance rather than the stenosis would therefore limit the increase in flow and there would be no apparent limitation to an increase in flow caused by the stenosis in that patient. However, if a normal coronary flow reserve in the absence of a stenosis were assumed to be five as a standardized condition, then the severity of a stenosis could be described in terms of limited coronary flow reserve for comparison with other stenoses independent of that patient's other physiologic variables. A similar argument can be made for each of the other physiologic variables affecting coronary flow reserve, such as coronary flow at rest and the extent of collateralization.

Standardized conditions. Thus, to compare severity of stenosis in different individuals or of the same stenosis at different times, coronary flow reserve should be determined under assumed standardized conditions even if those conditions are not actually present in a given patient. The most useful or representative standardized conditions would be a mean aortic pressure of 100 mm Hg, a normal maximal coronary flow of five times levels at rest, a coronary flow velocity at rest of 15 cm/s and the assumption of no collateral flow. By assuming these standardized conditions for our analysis, stenosis severity could be defined in various patients regardless of a wide variety of physiologic conditions ranging from hypertension to no blood pressure (dead) or from no collateral flow to that equal to normal arterial flow. We refer to this approach as component analysis; that is, one component of the coronary vascular system, the stenosis, is analyzed as if separate from the rest of the system and under standardized conditions.

On the other hand, if one wished to ask what was the actual coronary flow reserve in a given patient with a stenosis of known configuration, it would be necessary to directly measure the physiologic conditions affecting coronary flow reserve, such as pressure, normal maximal coronary flow, flow velocity at rest and the amount of collateral flow. Therefore, the poor correlation between individual stenosis dimensions and measured coronary flow reserve reported by others (23–25) might be expected not only because of incomplete fluid dynamic analysis of the stenoses but also because physiologic conditions other than stenosis configuration affecting coronary flow reserve may not have been standardized or accounted for. The use of standardized physiologic conditions in determining coronary flow reserve from a given stenosis configuration is a way of compartmentally analyzing the stenosis separately from the rest of the cardiovascular system in intact subjects.

Collateral flow. The physiologic variable of collateral flow in particular requires more detailed discussion. For purposes of illustrating a point, let us hypothesize that the vascular bed supplied by a stenotic coronary artery had a large amount of collateral flow from another normal artery. In this case coronary flow reserve measured in the coronary artery directly by flowmeter might be different from (less than) myocardial perfusion reserve measured by radiolabeled microspheres to the extent that perfusion was supplied by collateral flow. Mullani (42) has analyzed the relation between coronary artery flow reserve and myocardial perfusion reserve. Thus, under the assumed standardized conditions excluding collateral flow, the X-ray–predicted coronary artery flow reserve might then be in error compared with directly measured myocardial perfusion reserve in that subject. However, it would not be erroneous if the stenosis itself were analyzed separately from the rest of the cardiovascular system as if in the absence of collateral circulation. Only by such compartmental analysis of a stenosis independent of the collateral supply could its severity be established, as if in comparison with other stenoses in other subjects under standardized conditions of no collateral flow. In other words, stenoses of equal geometric severity have different functional effects depending on the physiologic condition of collateral channels independent of configuration. Comparison of the functional effects of stenoses then requires standardized physiologic conditions if the functional effects are to reflect differences in geometric severity only.

Aside from this logic, even well developed collateral vessels do not increase flow nearly to the extent of normal coronary arteries after potent coronary vasodilators. We therefore examined the maximal theoretical potential difference between coronary artery flow reserve and myocardial perfusion reserve for several different levels of stenosis severity assuming well developed collateral flow sufficient to provide normal perfusion at rest. Figure 6 shows this comparison of coronary artery flow reserve with myocardial perfusion reserve. For a 90% area reduction in arterial lumen in the presence of sufficient collateral channels to supply normal perfusion at rest, coronary artery flow reserve would be 2.0 whereas myocardial perfusion reserve would be 2.5. The error in predicting myocardial perfusion reserve from X-ray film analysis would therefore potentially be 0.5/2.5 or 20%. With more severe stenosis the error may become larger because collateral flow becomes a proportionately larger part of normal perfusion at rest.

Although it might be expected that directly measured myocardial perfusion reserve would be somewhat higher than that predicted by stenosis dimensions, it may not be much higher as suggested by our analysis and by Roth et

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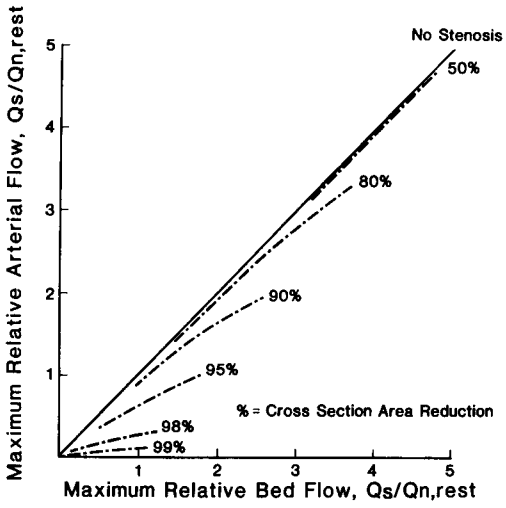

Figure 6. Relation between coronary artery flow reserve and myocardial perfusion reserve for stenoses of different levels of severity in the presence of collateral flow sufficient to provide normal coronary flow at rest. As an example, for a 90% area reduction in arterial lumen under these conditions, coronary artery flow reserve would be 2.0 whereas myocardial perfusion reserve would be 2.5 predicted theoretically.

al. (15). The explanation may be that maximal vasodilation frequently produces myocardial steal with *decreased* rather than increased flow to the vascular bed supplied by collateral flow. Therefore, it could be argued that the X-ray film determination of coronary flow reserve may remain quantitatively correct even in the presence of collateral circulation. However, the effects of collateral flow require further study.

Dynamic stenoses. Another physiologic variable that might potentially affect the relation between measured and X-ray–determined coronary flow reserve is dynamic change in stenosis severity (11,12,43). Coronary artery spasm, worsening percent narrowing or collapsing stenoses may cause changes in stenosis configuration and therefore in coronary flow reserve. Such changes in configuration would have to be measured by arteriograms taken during the state of altered configuration to determine the corresponding altered coronary flow reserve. However, the basic relation between configuration and flow reserve should remain as previously shown.

Vascular bed size. The final difficulty in interpreting quantitative arteriography in functional terms relates to the size of the distal vascular bed and the absolute arterial diameter. Even if all the dimensions of a stenosis are known, including absolute diameter, one does not know what the absolute diameter of the artery normally should be (or was, in the absence of atherosclerosis) to supply that distal vascular bed with adequate flow. In other words, even if quantitative arteriography could precisely predict what coronary flow and distal coronary pressure were at a given aortic pressure, one would not know whether that blood flow was appropriate for the vascular bed size. This problem also relates to where absolute dimensions are measured. A given absolute dimension may be normal for a distal segment of coronary artery but would indicate severe narrowing if present more proximally in that artery. Coronary flow reserve theoretically accounts for diffuse disease of an artery. It would be decreased in a diffusely narrowed artery relative to the size of its distal vascular bed. By comparison, a normal artery of equal size relative to its smaller distal bed would have a normal coronary flow reserve.

Conclusions. Coronary flow reserve is a single integrated measure of all the geometric characteristics of a stenosis. It can be predicted by quantitative coronary arteriography under standardized physiologic conditions as a way of compartmentally analyzing the stenosis itself separate from the rest of the cardiovascular system. In any given subject, coronary flow reserve can also be predicted from stenosis configuration for that specific subject provided pressure is measured, maximal vasodilation is achieved and normal coronary flow velocity at rest is assumed to be 15 cm/s. Myocardial perfusion reserve or coronary flow reserve may also be potentially measured directly by positron tomography in humans or by radiolabeled microspheres or implanted flowmeters in animals depending on clinical or experimental circumstances. However, such direct measurements would be affected by physiologic conditions independent of the stenosis configuration. Therefore, to utilize directly measured coronary flow reserve for assessing stenosis severity in an individual subject, these physiologic conditions would have to be standardized or accounted for.

Although these results validate the concept of coronary flow reserve as a single measure of stenosis severity accounting for all its geometric characteristics, the clinical application of that concept depends on what question is being asked about coronary flow reserve and on an understanding of the physiologic as well as anatomic factors affecting it. If the clinical question asks about severity of stenosis as such, then coronary flow reserve should be predicted from stenosis configuration using standardized assumed physiologic conditions to eliminate the effects of variable physiologic conditions affecting coronary flow reserve separate from stenosis configuration. If the clinical question asks about the effects of stenosis severity in a given individual under given conditions, then those physiologic conditions affecting coronary flow reserve, in addition to stenosis configuration, must also be measured or accounted for, or both. Failure to identify these two points of view, not previously recognized in the literature, has caused controversy in how to assess stenosis severity. For either point of view, we have demonstrated the concept that coronary flow reserve is a single integrated measure of stenosis severity and have defined the relation between anatomic characteristics of coronary stenoses and their functional hemodynamic effects.

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Appendix

The purpose of this Appendix is to derive a relation between stenosis configuration and coronary flow reserve. To do so, consider the schematic in Figure 2, illustrating a stenosis in the coronary system with a pressure source, aortic pressure (P_a), a stenotic artery with flow (Q) through it, a pressure distal to the stenosis, coronary perfusion pressure (P_c), a distal bed with a resistance (R) and an effective coronary back pressure (P_v) which is the critical closing pressure of the vascular bed or coronary venous pressure, whichever is higher. The resistance (R) is a lumped value for the combined total resistances of all blood vessels distal to the stenosis (distal coronary artery, arterioles, capillaries, venules and veins) as caused by both intravascular flow phenomenon (viscous shear) by extravascular compression and by vascular smooth muscle tone.

Flow through the coronary vascular bed can be described by the following conventional equation:

$$Q = \frac{P_c - P_v}{R}. \quad (1)$$

Under conditions of maximal coronary dilation in the absence of a stenosis, this equation becomes:

$$Q_{n,m} = \frac{P_a - P_v}{R_m}, \quad (2)$$

where $Q_{n,m}$ is normal maximal coronary flow and R_m is minimal coronary vascular resistance during maximal coronary vasodilation.

Coronary flow reserve (CFR) is defined as the ratio of maximal to resting flow (Q_m/Q_r), where Q_r is coronary flow at rest as follows: $CFR = Q_m/Q_r$. In the absence of a stenosis, normal coronary flow reserve is defined as follows: $CFR_n = Q_{n,m}/Q_{n,r}$, where CFR_n is the normal coronary flow reserve at a given aortic pressure in the absence of a stenosis.

Equation 2 can then be rewritten as:

$$Q_{n,r} = \frac{P_a - P_v}{R_m}\frac{1}{CFR_n}, \quad (3)$$

where $Q_{n,r}$ is normal coronary flow at rest in the absence of a stenosis. With a stenosis present, flow expressed in relative terms as a ratio to flow at rest, $Q/Q_{n,r}$ is obtained by dividing Equation 3 into Equation 1, yielding:

$$\frac{Q}{Q_{n,r}} = CFR_n \frac{P_c - P_v}{P_a - P_v}\frac{R_m}{R},$$

which can be arranged to give the following:

$$P_c = \frac{P_a - P_v}{CFR_n}\frac{R}{R_m}\frac{Q}{Q_{n,r}} + P_v. \quad (4)$$

This equation has the form as follows: $y = mx + b$, where y is the distal coronary pressure (P_c), x is coronary flow expressed as a ratio to the normal flow at rest ($Q/Q_{n,r}$), m is the slope of the pressure flow relation characteristic of the myocardial bed and P_v is the pressure at which flow ceases. The behavior of Equation 4 is depicted in Figure 7A as a family of lines representing different degrees of coronary vasodilation, that is, for various values of R/R_m. The heavy solid line indicates the condition of maximal vasodilation such that in Equation 4, $R/R_m = 1$. The slope of the pressure flow relation for the myocardial vascular bed is then $(P_a - P_v)/CFR_n$. Myocardial vasoconstriction relative to maximal vasodilation would then be represented by lines of increasing slope where $R/R_m > 1$.

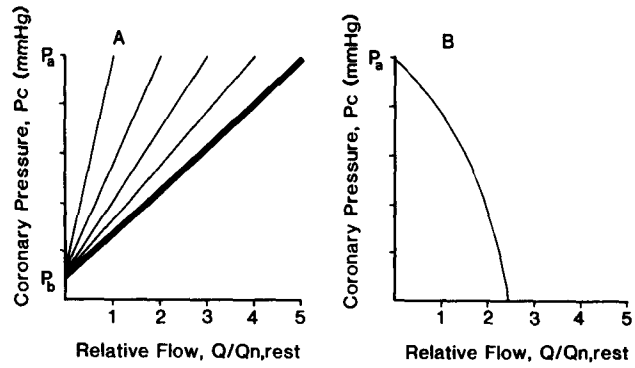
The effect of a coronary stenosis is to decrease coronary pressure (P_c) below its normal aortic pressure value by the amount of the stenosis pressure drop (ΔP), that is,

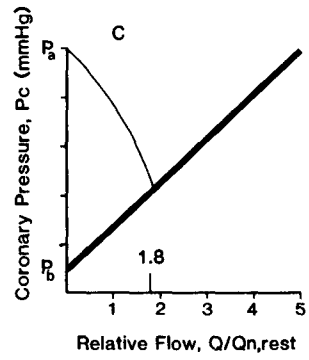
$$P_c = P_a - \Delta P. \quad (5)$$

Extensive studies (4,12,22) have shown that the pressure drop across a coronary stenosis is described by an equation having the general form:

$$\Delta P = fQ + sQ^2, \quad (6)$$

Figure 7. A, Relation between coronary flow and coronary perfusion pressure (Pc) under conditions of maximal coronary vasodilation is indicated by the **heavy solid line** (38). P_a = normal aortic pressure; P_b = back pressure in an occluded coronary artery. **B,** Relation between distal coronary perfusion pressure (Pc) and coronary flow is expressed as a ratio to normal flow at rest for a coronary artery stenosis (Q/Qn, rest). This **line** represents the distal coronary perfusion pressure resulting from the pressure gradient across the stenosis which in turn is determined by stenosis configuration. **C** is a superimposition of the graphs in **A** and **B**. The intersection of the two graphs gives the coronary flow reserve (1.8) for that particular stenosis of known dimensions and that coronary vascular bed under conditions of maximal coronary vasodilation.





where fQ represents pressure losses due to viscous wall shear along the stenotic lumen and which are linearly related to the flow rate through the stenosis (Q) and where sQ^2 reflects pressure losses associated with the abrupt expansion and deceleration of the flow as it exits the stenosis as related to the square of the blood flow. The coefficients f and s are determined by the detailed configuration of a coronary stenosis (that is, its length, axial and cross-sectional shapes, the diameter of the normal artery, the minimal cross-sectional area of the stenosis); f and s are also related to the viscosity and density of blood but these are relatively constant in most circumstances. We have previously shown that the coefficients f and s in Equation 6 can be accurately predicted by quantitative coronary arteriography (4,12,22).

Combining Equations 5 and 6 produces the coronary pressure that can be maintained for a given pressure and coronary stenosis, that is:

$$P_c = P_a - fQ - sQ^2. \quad (7)$$

To express flow relative to control at rest, these pressure loss terms can be multiplied and divided by $Q_{n,r}$ to make the terms in Equation 7 comparable with those in Equation 4:

$$P_c = P_a - f\,Q_{n,r}\left(\frac{Q}{Q_{n,r}}\right) - s\,Q_{n,r}^2\left(\frac{Q}{Q_{n,r}}\right)^2. \quad (8)$$

The graphic form of this equation is plotted in Figure 7B. As (relative) coronary flow increases, the distal coronary pressure decreases nonlinearly due to the pressure losses across the stenosis until maximal coronary vasodilation is reached. As shown in Figure 7C, which plots Equations 4 and 8 simultaneously, this flow-limiting condition occurs when the pressure-flow curve for the stenosis (Equation 8, Fig. 7B) intersects the pressure-flow relation for the maximal vasodilated distal bed without a stenosis (Equation 4 with $R/R_m = 1$ and heavy line in Fig. 7A). That intersection point gives the coronary flow reserve for that stenosis at that distal coronary vascular bed under conditions of maximal coronary vasodilation.

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